

PROTOCOL #ORTOPLAK

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Title of Study: Efficacy of the disclosing plaque agent as a guide to remove the oral biofilm in orthodontic patients: a Randomised Controlled Trial study.

Type of Study: Clinical

Protocol No: PROTOCOL #ORTOPLAK

Expected study start date: September, 2019 (study initiation)

Study Location/Country: Brescia, Italy

Study Originator(s)/ Contact (name, phone, fax): Magda Mensi, Piazzale Spedali Civili 1, 25123 Brescia, phone: +390303995784, email: magda.mensi@unibs.it

Test Products w/ PDM Numbers:

CE marked Medical Device to be used as a guided to professional oral hygiene in orthodontic patients (Confidential information)

<u>Study Title:</u>	Efficacy of the disclosing plaque agent as a guide to remove the oral biofilm in orthodontic patients: a Randomised Controlled Trial study
<u>Study sites:</u>	Dr.ssa Magda Mensi (lead site) University-Hospital of Brescia Brescia, Italy
<u>Study Phase:</u>	IV
<u>Name of Medical Device:</u>	Biofilm Discloser® (EMS Electrical Medical Systems SA, CH 1260-Nyon, Switzerland)
<u>Objective:</u>	The objective of the clinical study is to assess the efficacy of disclosing plaque agent as a guide to remove biofilm and plaque in orthodontic patient during professional oral hygiene performed with AirFlow® Plus powder and Airflow® Prophylaxis master (EMS Electrical Medical Systems SA, CH 1260-Nyon, Switzerland)
<u>Patient Population:</u>	32 orthodontic patients, systemically healthy, male and female adults (18 – 75 years) with plaque index above the 25%, without periodontal disease
<u>Structure:</u>	Parallel arms: Number of treatments: 1 (one guided by disclosing agent, one without) Duration of study: 6 months
<u>Number of Centers:</u>	One
<u>Blinding:</u>	Examiner-Blind
<u>Method of Patient Selection:</u>	Orthodontic patients with plaque index above the 25% without periodontal disease
<u>Total Sample Size:</u>	32 adult subjects will be recruited (randomized) to participate in this study, with 32 expected to complete the study
<u>Primary Efficacy Variable:</u>	Primary outcome measure will be the percentage of area in which the disclosing plaque agent is present (RPA: Residual Plaque Area) in both groups after professional oral hygiene

**Efficacy of the disclosing plaque agent as a guide to remove the oral biofilm in
orthodontic patients: a Randomised Controlled Trial study.**

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Protocol Date: Oct 29, 2019

Protocol Approval

Signature Page

Dr. Magda Mensi
University-Hospital of Brescia, Italy

Date

ADDRESSES AND RESPONSIBILITIES

Addresses

Study Centres:	Section of Periodontics, School of Dentistry, Department of Surgical Specialities, Radiological Science and Public Health University of Brescia Piazzale Spedali Civili 1 25123, Brescia, Italy
	Dr.ssa Magda Mensi (Principal Investigator) Tel. +390303995784 Email: magda.mensi@unibs.it
Study coordinator:	Dr.ssa Magda Mensi Section of Periodontics, School of Dentistry, Department of Surgical Specialities, Radiological Science and Public Health University-Hospital of Brescia Brescia, IT
Data Management & Monitoring:	Dr.ssa Magda Mensi Section of Periodontics, School of Dentistry, Department of Surgical Specialities, Radiological Science and Public Health University-Hospital of Brescia Brescia, IT
Statistician:	Prof. Stefano Calza Unit of Biostatistics and Bioinformatics, Department of Molecular and Translational Medicine University of Brescia Brescia, IT

Responsibilities

The **principal investigator's** responsibilities are described in detail in ISO norm 14155:2011 for the clinical investigation of medical devices for human subjects.

The role of the principal investigator is to implement and manage the day-to-day conduct of the clinical investigation as well as ensure data integrity and the rights, safety and well-being of the subjects involved in the clinical investigation.

The principal investigator shall be qualified by education, training and experience to assume responsibilities for the proper conduct of the clinical investigation. In particular, the principal investigator is responsible for:

- qualification of investigation site;
- communication with Ethics Committee;
- compliance with Informed Consent process;
- compliance with Clinical Investigation Plan.

Under the direct supervision of the Principal Investigator, certain duties may be delegated during the course of the study. These responsibilities will be documented on the transfer of responsibilities form maintained in the Investigator Site file.

The **Statistician** will be responsible for:

- sample size calculation;
- statistical plan;
- statistical section of the protocol;
- statistical evaluation;
- final statistical report.

OBJECTIVE

The study will be performed to assess the efficacy of disclosing plaque agent as a guide to remove biofilm and plaque in orthodontic patient during professional oral hygiene performed with air-polishing with Erythritol and ultrasonic device (guided biofilm therapy (GBT)).

INTRODUCTION

In the mouth of the patients the biofilm is not always evident, so it's removal can be difficult.

Using the disclosing plaque agent before the therapy as a guide to remove the biofilm may be a solution. Thanks to this tool, we can clearly see where the plaque is, so it's removal can be easier.

In orthodontic patients is more difficult to remove biofilm and plaque cause of braces that are an obstacle to a correct oral hygiene. Probably, using a disclosing plaque agent that guide the operator, could give more security for a better removal of the biofilm.

For this reason, we decided to study the efficacy of this method.

STUDY OUTCOMES

Primary outcome measure: the percentage of area in which the disclosing plaque agent is present (RPA: Residual Plaque Area).

RPA: residual plaque area: percentage of area with residual plaque coloured by disclosing plaque agent. This will be calculated with a ImageJ Software.

STUDY POPULATION

Thirty-two (32) adults, aged 18-75 years, will be entered into study (randomized). It is expected that all thirty-two (32) subjects will complete the study.

Randomized subjects who deviate from the protocol (major protocol deviation) and, for this reason, are excluded from the analysis, will be replaced to guarantee that the sample required for the analysis (32) is reached.

Patient will be treated at the Department of Surgical Specialities Radiological Science and Public Health, School of Dentistry, Section of Periodontics, Brescia, Italy from 05/2020.

Inclusion Characteristics

- Signed Informed Consent Form;
- Male and female subjects, aged 18-75 years, inclusive;
- Presence of orthodontic appliances;
- Good general health (free of systemic diseases such as diabetes, HIV infection or genetic disorder, ongoing malignant disease of any type that could influence the outcome of the treatment and might interfere with the evaluation of the study objectives);
- Generalized gingivitis;
- Plaque index (PI) above 25%;
- Availability for session of the study for an assigned subject;
- Presence of all inferior and superior anterior teeth from canine to canine;
- Smoking less than 10 cigarettes a day.

Exclusion Characteristics

- Chronic obstructive pulmonary disease and asthma;
- Patients with periodontally disease defined as presence of PPD \geq 4mm and /or PAL of \geq 3mm;
- Splinted teeth;
- Presence of prosthesis;
- Tumors or significant pathology of the soft or hard tissues of the oral cavity;
- Current radiotherapy or chemotherapy;
- Pregnant or lactating women;
- History of allergy to Erythritol;
- History of adverse reactions to lactose or fermented milk products;
- Restorations on the teeth to be treated which may interfere with treatment administration and/or scoring procedures, at the discretion of the examiner;
- Not willing to follow the agreed protocol.

Included subjects should not wash their teeth for 24 hours before the clinical examination.

Only the inferior and the superior frontal teeth from canine to canine will be included in the study but the professional oral hygiene will be done in full mouth.

A written informed consent will be obtained from each included patient after explanation of the risks and benefits of participating to this study. No change in the trial design will be made after approval of the Ethical Committee.

1. STUDY DESIGN

The study design was chosen according to the current standards required by ISO, GCP and according to national requirements.

- a. A Parallel-Arm, Examiner-Blinded, RCT will be established;
- b. The RCT will be run as mono-center;
- c. A total of 32 subjects will be recruited to participate in the study. It is expected that all of 32 subjects will complete the study in total;
- d. Admission into the study will be via rolling admission (estimated recruitment time: 6 months);
- e. Each subject must have orthodontic appliance, PI $>$ 25% and PPD $<$ 4mm;

- f. Each subject will follow the following treatment protocol:
- i. - Visit (T0): consent secured; screening and entry into study; baseline data collection, including full periodontal charting, (full-mouth PD, BOP, O'Leary PCR); randomization into one of the two treatment arms as per the randomization protocol;
 - ii. - Treatment (T0): all patients will receive a full-mouth periodontal treatment. Procedures will be performed in the following chronological sequence:
 - A. According to the randomization list, patients assigned to the **test group** will do professional oral hygiene guided by disclosing plaque (GBT):
 - Placement the disclosing plaque agent (Biofilm Discloser® (EMS Electrical Medical Systems SA, CH 1260-Nyon, Switzerland)) on the teeth and rinse with only water;
 - Tissue decontamination with Air-flow (Air-flow® Prophylaxis Master EMS, Nyon Switzerland) and erythritol powder (PLUS powder® EMS, Nyon Switzerland);
 - Supragingival removal biofilm with Air-flow (Air-flow® Prophylaxis Master EMS, Nyon Switzerland) and erythritol powder (PLUS powder® EMS, Nyon Switzerland);
 - Subgingival removal biofilm with Air-flow (Air-flow® Prophylaxis Master EMS, Nyon Switzerland) and erythritol powder (PLUS powder® EMS, Nyon Switzerland);
 - Calculus removal with piezoceramic device (Air-flow® Prophylaxis Master EMS, Nyon Switzerland), with a slim tip (PS® EMS, Nyon Switzerland);
 - The treatment ends, when all the disclosing plaque has been removed;
 - Placement of the disclosing plaque agent (Biofilm Discloser® (EMS Electrical Medical Systems SA, CH 1260-Nyon, Switzerland)) on the teeth and rinse with only water;
 - Collection of the pictures.
 - B. According to the randomization list, patients assigned to the **control group** will receive professional oral hygiene without the guide by disclosing plaque. The treatment as same as test group without the use of disclosing plaque at the beginning.

All the pictures collected will be analysed with a ImageJ Software to evaluate percentage of remaining plaque.

- g. All treatments are made by the same clinician (examiner);
- h. Calibration: the examiner should be calibrated measuring PPD and PAL in one quadrant with at least 6 teeth on 10 patients. Measurements should be repeated after one hour and variability should be assessed;

- i. Data collection: A PCP-UNC 15 periodontal probe is used on six sites per tooth (mesio-buccal, buccal, disto-buccal, mesio-lingual, lingual and disto-lingual) with a gentle probing force by the same examiner. Measurements are rounded to the nearest millimetre;
- j. Clinical assessment data will be recorded via hard copy CRFs. CRFs will be submitted to a data entry staff member for entry into the statistical database. At the conclusion of the study, such statistical database will be submitted to the statistician for the preparation of the statistical analysis and the final study report.

2. TEST TREATMENTS

Biofilm Discloser[®] by EMS Electrical Medical Systems SA, CH 1260-Nyon, Switzerland will be delivered to the study center prior study start.

Specification of software analysis

The disclosing plaque could be used as guide for all periodontal therapy.

After professional oral hygiene in both group disclosing plaque agents will be apply for the software analysis. Even if only 12 teeth will be analyzed by the software, the professional oral hygiene will be done in full mouth. The software analysis is done only on the frontal teeth for the repeatability and standardization of images.

Concomitant Therapy

Medication and in Concomitant Medication aren't important to the study.

Blinding and Randomization

Blinding: The statistician will be blinded to the group identification (coded as A (test group) and B (control group)). The patient and the operator will know the treatment. The operator making the measurements on the pictures after the end of the treatment will not know to which group the patient belongs to.

Randomization: Sequence generation: using computer generated random numbers, centralized. The random allocation sequence was generated by using randomization list will be created using uninformative labels (A and B) using block randomization algorithm (block size=4) using software R and package randomizeBE.

Allocation concealment: Operators will know about the intervention to be delivered by opening a sealed envelope before start the intervention. Both groups will have the same envelope. A paper marked with the letters A or B will be placed inside.

Implementation: Sequentially sealed opaque envelopes will be provided by the study adviser.

3. **PROCEDURE**

Screening and Selection of Subjects

Subjects will report to the clinical facility and be screened by the dental examiner to identify those subjects who meet the inclusion/exclusion characteristics. The findings of this initial screening procedure will be recorded on the CRF. Subjects who meet the inclusion/exclusion characteristics and sign an Informed Consent Form will be entered into the study.

Baseline Oral Soft and Hard Tissue Assessment

All subjects will receive an evaluation of their oral soft and hard tissues. This examination will include an evaluation of the soft and hard palate, gingival mucosa, buccal mucosa, mucogingival fold areas, tongue, sublingual and submandibular areas and the tonsillar and pharyngeal areas. The results of this evaluation will be recorded on the CRF.

Clinical Periodontal Evaluation

All patients receiving treatment will be evaluated by the dental examiner for the following assessments (see Study Flow Chart):

- Full Mouth Plaque (O'Leary Plaque Control Record);
- Periodontal Inflammation via BOP Scores;
- Probing Pocket Depth;
- Clinical Attachment Level.

Clinical attachment level is the measurement of the position of the soft tissue in relation to the cemento-enamel junction (CEJ) that is a fixed point that does not change throughout life. All parameters will be recorded in the CRF.

Treatment

Patients who have been identified for treatment will be randomized according to a randomization table generated. The entire mouth will be treated (supra/subgingival) in a single session. If the patient has been identified to receive the control treatment, all teeth present will not receive the application of disclosing agent and will receive directly full-mouth supragingival and intra sulcular biofilm removal with Airflow and full mouth calculus removal.

If the patient has been identified to receive the test treatment, he/she will start full mouth with the application of disclosing plaque.

Study Flow Chart

Study phase	Enrolment
Study visit	
Selection criteria	+
Informed consent	+
Demographics, ethnics	+
General health status	+
Medical & dental history	+
Concomitant therapy/treatment	+
ENTIRE DENTITION - Plaque (O'Leary)	+
ENTIRE DENTITION - Probing parameters (PPD, BOP)	+
ENTIRE DENTITION - Clinical attachment level	+
Randomization	+
Supragingival and intra-sulcular biofilm removal with Airflow at sites with PD ≤ 4 mm	+
Supragingival calculus removal with ultrasonic device	+
Subgingival biofilm removal with USD at sites with PD> 4 mm, including the experimental sites	+
Application of disclosing plaque	+
Collect picture	+
Oral hygiene instructions	+

4. STATISTICAL ANALYSIS

Sample size determination

Sample size was computed assuming a two independent group comparison based on t-test allowing for different variances (Welch test). We assumed 5% and 10% residual plaque (percent of plaque are over total teeth inspected area) respectively and a 60% coefficient of variation for both groups. Considering a 80% power and a 5% significance level we computed a total sample size of $N = 32$ (16 for each group). To allow for potential deviations from normality assumption for proportions we also computed sample size using a simulation based on 2000 Monte Carlo samples from the null distributions (with parameters as specified above). A consistent estimate of $N = 30$ was achieved. We therefore settled on $N = 32$ (software: PASS 13).

Statistical Analysis

All data analysis will be carried out according to a pre-established analysis plan by a biostatistician blinded to group allocation. Comparison between treatments will be performed using independent sample t-Test.

All statistical comparisons will be conducted at the 0.05 level of significance.

Evaluation of Safety

The following safety variables will be used for the evaluation of safety:

- Adverse events (AE);
- Adverse reactions (AR).

The total number of AEs and the total number of AEs at least possibly related to the study treatment, as well as the total number of patients affected by at least one adverse event will be calculated per treatment group.

The type of AE classified by organ system (according to MedDRA terminology) will be tabulated. Serious and/or unanticipated adverse events and AEs resulting in discontinuation or reduction/withdrawal of the study treatment will be presented separately.

Safety analysis set

Safety summaries will be based on the safety analysis set which will consist of all patients who received the test/control treatment.

5. MONITORING AND AUDIT

Study Monitoring

The study will be monitored by the Principal Investigator at periodic intervals during the course of the study to ensure that the study is being conducted according to Good Clinical Practice.

The Investigators will be contacted by the PI on a regular basis. On this occasion, the progress of the study will be discussed with the Investigator and the CRFs will be checked for completeness and consistency and to verify compliance with the study protocol.

6. SUBJECT TERMINATION/WITHDRAWAL PROCEDURES

All efforts will be made to determine the reason(s) why a patient is withdrawn from the study. Subjects could be withdrawn from the study if any of the following occur:

1. Subject fails to substantially comply with the protocol requirements;
2. Subject develops a serious adverse reaction. The Study Investigator will immediately notify the PI and information will be recorded on a Serious Adverse Event Form (Appendix 3);
3. Subject elects to terminate participation in the study. Participation in the study is voluntary. A subject has the right to withdraw from the study at any time for any reason.

The Investigator may terminate the study at any time if the risk-benefit ratio is no longer favourable. Before discontinuation, the Investigator should inform the PI and ask for advice. If the Investigator is concerned about continuation of the study, his/her concerns should be transmitted immediately to the PI.

7. DOCUMENTATION AND DATA MANAGEMENT

Data collection in the case report form (CRF)

All study data will be recorded in the case report forms identified by the subject number. Only the principal investigator, co-investigators, or designated study personnel may make entries in the case report forms.

The Investigator has to identify all data that were directly recorded into the CRF and to be considered to be source data.

The CRFs will be checked for completeness and plausibility by the PI. The Investigator will resolve any queries.

Investigator Site File (ISF)

The ISF includes all documents that are required for the clinical study. During monitoring, the ISF will be checked regularly for completeness and actuality. After the clinical trial is finished or stopped, the ISF has to be stored 15 years in the study center.

Data Management

Data extraction from CRFs into a single, electronic database is performed by examiners. Discrepancies are to be clarified and corrected by authorized persons by means of documented data queries between Statistician and Investigator(s).

After the study is finished and before data are analyzed, a blind data review meeting will be held between the investigator and the statistician. When the database has been declared to be complete and accurate, it will be locked. Any changes to the database after this procedure can only be made by joint written agreement among the clinical trial leader, the trial statistician, and the co-investigators.

8. ADVERSE EXPERIENCES/EVENTS

Subjects will be informed of any possible adverse reactions which they could experience and will be instructed to immediately report any event to the investigator. The investigators will record any and all adverse reactions and report this documentation to the Principal Investigator. In the event of an adverse experience, emergency or other problems or questions regarding participation in this study, the subject can contact the following investigators:

for Brescia Site: Dr.ssa Magda Mensi (Principal Investigator) – tel. +39 030 3995784.

Adverse Events (AEs) and Serious Adverse Events (SAEs) are defined by the ICH Guideline Medical Device Directive 93/43/EEC and Guidelines on Medical Devices MEDDEV 2.7/3rev. 3, May 2015 Clinical Investigations: Serious Adverse Event Reporting under Directives 90/385/EEC and 93/42/EEC for Good Clinical Practice (ICH GCP) as follows:

An adverse event (AE) is any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the investigational medical device.

With respect to intensity, adverse events are classified as follows:

- Mild Some awareness of symptoms, but easily tolerated;
- Moderate Symptoms causing enough discomfort to interfere with usual activity;
- Severe Incapacitating event causing inability to work or to perform usual activity.

Adverse events are classified as either non-serious or serious.

Serious Adverse Event (SAE) is an adverse event that:

- a) led to a death;
- b) led to a serious deterioration in health of the subject, that either resulted in:
 - a life-threatening illness or injury, or
 - a permanent impairment of a body structure or a body function, or
 - in-patient hospitalization or prolongation of existing hospitalization, or
 - in medical or surgical intervention to prevent life threatening illness or
 - injury or permanent impairment to a body structure or a body function.
- c) led to fetal distress, fetal death or a congenital abnormality or birth defect.

Device deficiency: inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer.

AEs include any clinically significant deterioration of a subject's medical status, after being enrolled and signing an informed consent form. The AE may involve any organs or systems and can be represented by the new onset or the deterioration of a disease, a syndrome, a symptom, a physical sign, as well as by findings and results of instrumental examinations and laboratory tests. Any medically relevant and untoward change from baseline, including frequency or pattern changes for a fluctuating condition (e.g., migraine), occurring after the administration of investigated treatments is an adverse event. All such occurrences must be recorded and reported accordingly, whether they appear causally related to the study medication, or not.

Serious Adverse Device Effect (SADE) is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Unanticipated Serious Adverse Device Effect (USADE) is a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report or investigator's brochure (IB).

NOTE: Anticipated SADE (ASADE): an effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report or IB.

The following events are considered reportable:

- any SAE;
- any Device Deficiency that might have led to a SAE if:
 - a) suitable action had not been taken or
 - b) intervention had not been made or
 - c) if circumstances had been less fortunate;
- new findings/updates in relation to already reported events.

Reportable events have to be reported by clinical investigators.

Assessment of Causality

The following criteria are to be used for the assessment of the causal relationship to the test/control treatment. For classification, all criteria of one of the following categories must be met:

related, if

- a timely correlation exists and
- dechallenge and/or rechallenge and
- a biological plausibility exists and
- other factors are clearly excluded
- a medical report or clinical proof exists;

possibly related, if

- a timely correlation exists and
- dechallenge and/or rechallenge and
- a biological plausibility exists and

- a medical report or clinical proof does not exist;

unrelated, if

- a timely correlation does not exist or is uncertain and
- dechallenge and/or rechallenge does not exist and
- a biological plausibility exists and
- a medical report or a clinical proof does not exist;

unknown, if

- not enough information exists for evaluation;
- no further contact with reporter possible.

Sound medical/clinical judgment will be applied when assessing the causality and seriousness of the adverse events.

Adverse Event Reporting

The study center will provide the study participants with emergency telephone numbers for study related support and feedback. The emergency telephone number is operated by either an investigator of the study or by a qualified person designated by the principal investigator. The schedule of reachability of the emergency telephone number will be defined prior to start of the study.

Serious Adverse Events

The Investigator shall immediately after awareness (and in any event, not later than within 24 hours after awareness) inform the PI. The Investigator will send the SAE report to the following email address: magda.mensi@unibs.it. Appendix 3 has to be used for SAE reporting. Form has to be completed electronically and in English.

Adverse Events

Adverse events will be assessed by the investigator or designee within 24 hours for severity, relationship to the study product, possible etiologies, and whether the event meets the criteria as a serious adverse event and therefore requires immediate notification to the PI. For data collection purposes, the outcome of all adverse events recorded on the Adverse Reaction section of the CRF will be designated as of the completion of the final evaluation or examination. However, the

investigator is responsible for following all adverse events until resolution or until no longer of clinical concern, and providing these data to the PI. At the end of the study, the investigator will report all adverse events (serious and non-serious) to the PI on CRFs. Forms have to be completed electronically and in English.

Pregnancy

No pregnant women (according to medical history) will intentionally be enrolled in this study. In the event a woman enrolled in this clinical research study becomes pregnant during the course of the study, participation in this study will be terminated upon the clinical staff's notification of the event. The subject's medical records used in this study will be updated to reflect the pregnancy and there will be follow-up contact until the end of the pregnancy to record the outcome in the clinical file.

9. ADHERENCE TO PROTOCOL/AMENDMENT(S)

The Investigator will be required to adhere to the final protocol. Any changes to the protocol, except those necessary to eliminate apparent hazards, will require prior approval by the local reviewers through the submission of a protocol amendment. In the event of emergency, the Investigator shall engage any medical procedures that he/she deems appropriate. However, all such procedures must be promptly reported to the PI and Ethical Committee.

The Ethical Committee which granted approval for the study must be notified of all changes in the protocol and must provide written approval if changes are substantial (e.g. increase the risk to the subject, and/or affect the rights of the subject or validity of the investigation, change of/within study population, number of participants or changes of patients' age group).

Departures from eligibility requirements may be allowed on a case-by-case basis by the medical monitor or other authorized sponsor representative. Such departures must be medically and scientifically justified, must be pre-authorized, and must be documented in the CRF and tracked as official eligibility waivers.

10. ADMINISTRATIVE ASPECTS

Final Report

Following the completion of the study, the PI shall prepare a final study report. The final report will include a general description of the conduct of the study including protocol deviations, subject withdrawals, discussion of any adverse events, safety and efficacy data, and statistical analysis of the data. This report will be shared with the Co-investigator at the Participating Centre by the Principal Investigator, and agreed upon parts before being sent to the Sponsor.

Data Retention

The information in this and any further document contains trade secrets and commercial information that are privileged or confidential and may not be disclosed unless such disclosure is required by law or regulations.

In any event, persons to whom the information is disclosed must be informed that the information is privileged or confidential and may not be further disclosed by them.

The files pertaining to this study will be kept by the University-Hospital of Brescia for a period of 15 years from the day of delivery of the final report and will be available for consultation by competent authorities at any time.

The Investigators will retain originals of the approved study protocol, copies of completed CRFs, subjects' participation agreements, relevant source documents and all other supporting documentation related to the study for a period of 5 years. These files must be made available for inspection upon reasonable request by an authorized representative of EMS or the competent authorities.

11. ETHICAL ASPECTS AND REGULATIONS

Ethical Conduct of the Study

This study is to be conducted in accordance with the ethical principles of the Declaration of Helsinki and according to local laws and regulations.

Independent Ethics Committee (IEC) and Relevant Authorities

Before starting the study, the study protocol will be subject to review by the Ethical Committee of the University-Hospital of Brescia. As required by law, the study will be notified to authorities if applicable. No subject should be admitted to the study before the Ethical Committees issue their written favourable opinion of the study. Periodic status reports must be reported to the ethics committee at least annually as well as notification of the completion of the study. The investigator must maintain an accurate and complete record of all reports and documents submitted to and received from the ethics committee according to the ISO 14155:2011 Clinical Investigation of Medical devices for human subjects.

Subject information and Informed consent form

The purpose and description of the study in lay language, possible adverse reactions, risks and benefits of participation and the subject's right to withdraw without prejudice at any time must be

explained to each subject. Each subject must read, understand and sign the informed consent form provided before any study-related procedure.

Subject data protection and Confidentiality

The name of the subject as well as all other personal data will be kept strictly confidential by the Investigator. If due to medical reasons, it is necessary to identify the subject during the study course, this will be done under medical secrecy.

The subject has given his/her consent before the beginning of the study. In case of withdrawal of this consent subject has to leave the study.

All subjects will agree to verify, by letter, that they participated in this study, if called upon to do so.

New Findings

Subjects will be informed of any significant new findings related to study products or procedures when they become known during the course of this clinical research study. Such information may affect the subject's decision to continue participation in the study.